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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

UNITED STATES DEPARTMENT OF COMMERCE
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	5

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on the 1st - Cardf

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☐ Claim(s) 71 - 114 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 71 - 114, 71 - 73 is/are rejected.
☒ Claim(s) 74 - 76 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Group 1640, Technology Center 1600.

2. ***Formal Matters:***

3. ***Double Patenting Rejections:***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 71-114 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the recently issued claims of copending Application No. 07/982255 and 08/336728. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are also obvious over the allowed and co-pending applications because the claims are sub-generic to the claims of the co-pending application, as these claims overlap in scope.

The allowed claims in the co-pending applications are directed to either the full length or mutated or fragments SCF polypeptides and/or pharmaceutical compositions thereto (not the above noted applications are in Issue Branch and not presently available, but it is clear that protein claims were allowed). In the event that either of the co-pending applications do not have claims to composition, it would have been prima facie obvious to formulate the various SCF polypeptide

of the co-pending application with a carrier or some other auxiliary agent for use therapeutically. The various means of formulation and delivery of the composition are well known in the art, and the artisan would also have found it obvious to prepare the SCF composition and formulate in a manner consistent with the well known teaching of the Remington's Pharmaceuticals Manual. Furthermore, it would have also been prima facie obvious to admix the SCF polypeptides with other cytokines for the advantage of achieving an additive or synergistic effect. It is also well known in the art that many cytokines possess the same, similar or over-lapping biological activities, and further known that combination therapies with one or more cytokines renders improve therapeutic effects. Additionally, at the time of the invention, it was also well known that many cytokines down-regulate or up-regulate the activity of other cytokines and that combined cytokine activities produce a cascade effect, thus further rendering obvious the combination of the SCF of the instant claims over the recently issued claims of the co-pending applications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Objections and 35 USC 112 Rejections:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 71-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly directed to fragments and analogs of the SCF protein, but the specification has not clearly defined the metes and bounds of the claims, nor has the specification provided a written description for these protein products, or the precise make-up of these

fragments and analogs. The specification fails to provide an adequate and/or specific written description for the broad products of the claims such as for fragments, functional derivatives, analogs and variants. As set forth in Reagents of the University of California v. Eli Lilly & Co. 119 F3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of the broad products of the claims such as for fragments and analogs "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, an adequate written description of a these broad protein products, requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it/making it; what is required is a description of these various protein products themselves (at 1170, 25 USPQ2d at 1606. (page 1404). Furthermore, the name of the broad products of the claims such as for fragments, functional derivatives, analogs and variants is not itself a written description of these products; it conveys no distinguishing information concerning their identity. Accordingly, the specification does not provide a written description of the invention of claim 5. (page 1405).

3b. Claims 71-73 and 79-102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the mature form of the SCF and certain fragmented forms or mutated SCF, does not reasonably provide enablement for: 1) compositions comprising any and all SCF fragments or any and all SCF analogs (claims 71-73); 2) nor is there enablement for compositions of SCF with the recitation of the various intended use limitations in claims 79-102. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success the invention commensurate in scope with these claims.

The specification is not commensurate in scope with the claims for compositions comprising any fragment or analog of the SCF, wherein these protein products are not sufficiently characterized and enabled by the claims. It is evident that the specification provides extensive teachings about the SCF, how to make it, and how to make various fragments and/or some analogs of the protein, however, this does not serve to enable the scope of the claims. Enablement for the claims can not merely be perfected by assuming that the protein can cleaved from one or both ends to obtain biologically protein fragments based on the fact that certain fragments and analogs have been prepared. There must be some guidance, the establishment of a nexus or a reasonable degree of predictability about where these regions are and how to obtain fragments or contiguous region of sufficient size that could be used for their intended purpose, a reasonable amount of assurance that the fragment and analogs will possess the desired activity.

The skilled artisan would be faced with an undue amount of experimentation for determining how long the fragments must be; from what region/portion on the protein the fragment covers, represents or corresponds to; does the fragment have to represent a contiguous string of amino acid residues on the protein's structure or is the fragment comprise a make-up of all or only portions of the mature protein's sequence, because knowledge of these and many variables with assurances that the fragment is biologically active would satisfy this requirement for enablement. However, this has not been provided and there is insufficient evidence about regions

needed for such things as cysteine bonds and receptor binding, and there are little/limited or no, teachings, conclusions and speculated that the instant fragment will possess the same or similar activities as the mature proteins or to other proteins that may be structurally or functionally related to it. The claims do not set forth any specific fragments that are identified by their size, specifically encoded amino acids residues, nor to the specific region on the protein that this fragment correspond to (e.g. the N- or C-terminal regions; if it is a fragment from an internal portion of the protein and what this specific portion is). While the claims state that the composition comprising the various fragments and analogs have to be biologically active, this is insufficient to enable the scope of the various fragments and analogs-particularly since no specific activity is recited that would further enable and define to broad limitations of fragments or analogs of the SCF.

Applicants can not merely rely on the issue of "make and test" to satisfy the enablement provisions for the breadth of the fragments presented in the claims. Rather, the skilled artisan would need to know more than just how to make the fragment from cleavage, but the artisan would need to necessarily know how to make the specific fragment with reasonable assurance that the various fragments would possess the desired activity and can be usable as such. Furthermore, there are little or no structure/function studies provided of record for the protein, thus, the skilled artisan does not know where the binding regions are; nor is it clear where usable epitopic/ antigenic regions are; where the thermal, enzymatic or other stability regions are; if all or part of the N-and C-terminals are necessary.

Since there is insufficient enablement for where the biologically active regions are, it would be difficult to determine what specific functional activity on the protein these fragments cover since many protein possess multiple biological activities, thus, the activity that the fragment(s) have to possess has not been set forth in the claims, nor enabled by the specification. All of these variables would have to be known for the skilled artisan to produce fragments that possess the desired properties and therefore be usable in a manner contemplated. Without such

information, the skilled artisan would have to resort to trial-and-error and be faced with undue experimentation for making and using the full scope of these fragments based on the limited characterization set forth in the specification, as well as the limited characterization that has been set forth in the claims for the fragments. There must be some guidance or a reasonable degree of predictability about where these regions are and how to obtain a fragment of sufficient size that could be used for its intended purpose.

As with the lack of enablement for compositions comprising the broad array of fragments as set forth above, the claim limitations for analogs, are also not enabled by the specification. The specification fails to provide enablement by way of sufficient examples, evidence or guidance that the various mutations within the scope of "analogs" can be made and that they would possess the desired structure or function. There are limited or little or no structure/function studies of record to ensure that the skilled artisan would know how to go about picking and choosing the appropriate residues for substitution at the designated location with a reasonable assurance that they will possess the desired structure and function without encountering undue experimentation. Multiple mutations are also encompassed by analogs, but the effects of one, two or more substitutions also has not been enabled by the specification. The effect of such multiple mutations would have a significant and non-predictive affect on the protein that has been shown to be highly conservative across specie line, which high degree of homology would suggest that the protein can only tolerate limited modifications without substantially altering the functionality of the protein. Therefore, in the absence of examples or sufficient guidance for the degree, nature and make-up of these multiple mutations, the specification does not enable the scope of the claims for analogs, functional derivatives or variants.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be

made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structural/ functional relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity. These various regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions, insertions or deletions), and the nature and extent of the changes that can be made in these positions in order to obtain the scope of the claimed peptides/proteins. Such extensive modifications might also read on previously characterized chemokine proteins since many of the chemokines of both the alpha and beta family possess a high degree of homology; alternatively, this might also include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above and In re Fisher, 166 USPQ 18.

The scope of applicant's claims encompass modification on the protein that would be critical as well as non-critical for the biological activity of the protein. Thus, even if **critical** residues were identified, which in this case they are not, the mere identification of these critical regions would not be sufficient as the ordinary artisan would immediately recognize that the modified site must assume the proper three-dimensional configuration to be active-which conformation is dependent upon surrounding residues. Even the substitution/insertion/deletion of non-essential residues can often destroy activity, therefore, it is deemed that to make each of the possible amino acid modifications for each of the non-essential residues, even if only conservative replacements were made, would <u>also</u> constitute undue experimentation. The introduction of non-

conservative substitution, non-naturally occurring amino acids, deletions or insertions further raises the possible number of species. Therefore Applicant has not presented enablement commensurate in scope with the claims.

4. Rejections Over Prior Art:

5. The claims are free of the prior art.

Claims 74-76 and 103-114 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph and the obviousness type double patenting rejection, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

6. Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1647, whose telephone number is (703) 308-4232.** Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800